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10/568,507	02/16/2006	Nobuko Yamamoto	03500.103811.	1163

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EXAMINER	
CROW, ROBERT THOMAS	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,507	YAMAMOTO, NOBUKO	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9-11 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 9-11, and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 14 June 2010 has been entered.

Status of the Claims

2. This action is in response to papers filed 14 June 2010 in which the previous after-final amendments to claims 22, 24, and 25 and certified translation were entered and claims 22 and 25 were further amended, no claims were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections.

Claims 1, 9-11, and 22-25 are under prosecution.

3. The following rejections are new rejections necessitated by the amendments and by the certified translation of the foreign priority document.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 9-11, and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Nature of the Invention and Breadth of Claims

Claims 1, 9-11, and 22-25 encompass the embodiment of Claim 22. Claim 22, upon which claim 24 depends, encompasses a probe carrier wherein the number of spots for a target substance corresponding the a gene expected to exist at a higher ratio

is larger than a number of spots for a target substance corresponding to a gene expected to exist at a lower number, based on average amounts of expression in humans. Claims 1, 9-11, and 22-25 also encompass the embodiment of Claim 25. Claim 25 encompasses a probe carrier wherein the number of spots in each of the areas is proportional to an average amount of expression in humans of a target gene.

Guidance in the Specification and Working Examples

It is noted that page 4 (lines 25-27) of the specification and original claim 8 discuss "average" expression, original claim 8 recites average expression in humans, page 21 (lines 25-27) of the specification discusses gene expression in human tissue, and the Figures depict embodiments of probe carriers merely as cartoon representations and do not show actual arrays produced based on average amounts of expression in humans. Thus, the specification provides no guidance as to the synthesis of a probe carrier wherein the number of spots in each of the areas is proportional to an average amount of expression in humans of a target gene. Further, the specification does not describe isolating nucleic acid and quantifying the amounts of expressed genes therein so as to generate a profile of "average" expression in humans in order to obtain proper spot ratios based on "average" expression in humans.

State of the Art, Relative Skill of Those in the Art, and Predictability or Unpredictability in the Art

The level of skill in the art regarding the synthesis of probe carriers (i.e., of nucleic acid molecules) is deemed to be high.

The prior art of Cheung et al (Nature Genetics, vol. 22, pages 422-425, March 2003) clearly indicates that there is natural variation of gene expression in humans (Title). Cheung et al also specifically teach that variance among unrelated individuals was 3-11 times greater than that between monozygotic twins, and that even variation among siblings (i.e., members of the same family) was 2-5 times greater than that between twins (page 424, column 1). Thus, the prior art of Cheung et al clearly indicates that the amount of gene expression varies considerably, even among members of the same family.

It is also noted that the prior art of Roman-Roman et al (Bone, vol. 32, pages 474-482 (2003)) clearly indicates gene expression patterns vary among different cell types (Introduction). Thus, the prior art of Roman-Roman et al clearly indicates that the amount of gene expression varies considerably among given cell types (i.e., even within an individual human).

Further, the prior art of Brodt-Eppley et al (Obs. & Gyn., vol. 93, pages 89-93 (1999)) indicates that gene expression among a group of pregnant women varied considerably (Table 1). Thus, the prior art of Brodt-Eppley et al clearly indicates that the amount of gene expression varies considerably among groups of patients during different stages of the same physiological condition (i.e., pregnancy).

In view of the teachings of the prior art, it is clear that there is no such thing as "average" expression in humans because the amount of expression not only varies among individuals who are actually related, but because the expression profile (i.e.,

amount) varies between different tissue types and because expression also varied among groups of patients during different stages of the same physiological condition.

In addition, the invention is drawn to probe carriers of nucleic acid molecules, which are biological molecules, and is therefore in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Degree of Experimentation

To practice the invention as it is claimed, the skilled artisan would have to perform numerous experiments to develop a plurality of specific and selectively functionalized areas to form the addressable features on a single bead-shaped substrate. Each experiment would itself comprise multiple steps, requiring experimentation for each of the many steps with no guarantee of success in any individual step, thereby demanding years of inventive effort for effective reduction to practice. Thus, the quantity of experimentation in this area would be extremely large since there are a significant number of parameters that would have to be studied. Furthermore, the ultimate outcome of such experimentation is completely unpredictable.

Conclusion

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement

provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in Genentech Inc. v Novo Nordisk 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the lack of specific working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention. Thus, claims 1, 9-11, and 22-25 are not enabled for embodiments wherein the number of spots for a target substance corresponding the a gene expected to exist at a higher ratio is larger than a number of spots for a target substance corresponding to a gene expected to exist at a lower number, based on average amounts of expression in humans (i.e., as embodied by claim 22), nor are claims 1, 9-11, and 22-25 enabled for embodiments wherein the number of spots in each of the areas is proportional to an average amount of expression in humans of a target gene. Claims 22 and 24-25 have a complete lack of enablement.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 10, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sheehan et al (Biosensors and Bioelectronics, vol. 18. pages 1455-1459, available online 2 April 2003; as evidenced by the Biosensors and Bioelectronics homepage at sciencedirect.com [retrieved on 2010-02-02]) in view of Ilsley et al (U.S. Patent Application Publication No. US 2004/0081969 A1, published 29 April 2004, filed 29 October 2002).

Regarding claim 1, Sheehan et al teach a probe carrier in the form of a biomolecule array, which has a gold surface (page 10456, Section 2.2) having separated spots at known locations on the carrier (Figure 2). The spots have a uniform diameter (page 1457, column 2, second full paragraph), and are produced from a 3 micromolar solution (page 1456, Section 2.2).

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not posses characteristic relied on" (205 USPQ 594, second column, first full paragraph). While Sheehan et al do

not explicitly teach each of the four different ssDNA probes in Figure 2 are spotted from solutions having the same concentrations, Sheehan et al only disclose one solution concentration for spotted DNA probes (page 1456, Section 2.2). Thus, Sheehan et al either teach all of the probes are spotted at the same concentration, or it would be obvious because Sheehan et al do not indicated that different concentrations are utilized.

Sheehan et al do not teach spots are for different genes, or that the number of spots differs depending on the genes.

However, Ilsley et al teach a probe carrier comprising a carrier in the form of a substrate having an array (Abstract) having thereon a plurality of probe spots (paragraph 0068). The array comprises a plurality of different spot patterns, corresponding to different genes, such that the number of different spot patterns is as great as the number of genes represented on the array (paragraph 0068).

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not posses characteristic relied on" (205 USPQ 594, second column, first full paragraph). Ilsley et al teach the each gene pattern is different, and that the patterns include a grid of spots across the substrate surface, curvilinear rows across the surface, concentric circles, or semicircles of spots. The different patterns are believed to contain different numbers; i.e., a straight

line (i.e., a grid) across the surface is believed to contain a different number of spots than curvilinear rows across the surface, a series of concentric circles, or semicircles.

Ilsley et al also teach the different spot patterns for different genes have the added advantage of allowing computer analysis of the data so that patient response to treatment can be monitored (paragraph 0004). Thus, Ilsley et al teach the known technique of having spots for different genes, and that the number of spots differs depending on the genes.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the probe carrier as taught by Sheehan et al so that the spots of the probe carrier comprise spots for different genes and so that the pattern of spots, and thus the number of spots, differs depending on the genes in accordance with the teachings of Ilsley et al to arrive at the instantly claimed probe carrier with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a probe carrier having the added advantage of allowing computer analysis of the data so that patient response to treatment can be monitored as explicitly taught by Ilsley et al (paragraph 0004). In addition, it would have been obvious to the ordinary artisan that the known technique of having pattern of spots for different genes, and thus different numbers of spots for different genes, as taught by Ilsley et al could have been applied to the probe carrier of Sheehan et al with predictable results because the known technique of having pattern of spots for different genes, and thus different numbers of

spots for different genes, as taught by Ilsley et al predictably results in probe numbers and spot numbers suitable for genetic assays.

Regarding claim 10, the carrier of claim 1 is discussed above. Ilsley et al teach the spots are formed by an ink-jet (i.e., pulse jet) method (paragraph 0072). Thus, modification of the carrier of Sheehan et al with the teachings of Ilsley et al results in a probe carrier wherein the spots are formed by an ink-jet (i.e., pulse jet) method.

In addition, it is noted that the courts have stated:

> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). See MPEP§ 2113.

The limitations of claim 10 are part of the process of making the probe carrier rather than structural limitations of the probe carrier. Because the prior art teaches the structural elements of claim 1, claim 10 is also obvious over the prior art.

Regarding claim 23, the carrier of probe 1 is discussed above. Ilsley et al also teach the amount of probes immobilized per spot is known; namely, 100,000 molecules/feature (i.e., probes per spot) is immobilized (paragraph 0067). Thus, modification of the carrier of Sheehan et al with the teachings of Ilsley et al results in a carrier wherein the amount of probes immobilized per spot is known.

8. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sheehan et al (Biosensors and Bioelectronics, vol. 18. pages 1455-1459, available online 2 April 2003; as evidenced by the Biosensors and Bioelectronics homepage at sciencedirect.com [retrieved on 2010-02-02]) in view of Ilsley et al (U.S. Patent Application Publication No. US 2004/0081969 A1, published 29 April 2004, filed 29 October 2002) as applied to claim 1 above, and further in view of Leproust et al (U.S. Patent Application Publication No U.S. 2004/0081967 A1, filed 25 October 2002).

Regarding claim 9, the carrier of claim 1 is discussed above in Section 7.

Neither Sheehan et al nor Ilsley et al teach the amount of probe molecules per spot is the same for the same probe and different between probes having different sequences; namely, features within a region have the same probe density and the different regions have different probe densities.

However, Leproust et al teach a probe carrier in the form of an array (Abstract0 having gene probes (paragraph 0001), wherein the amount of probe molecules per spot is the same for the same probe and different between probes having different sequences; namely, features within a region have the same probe density and the different regions have different probe densities (paragraph 0011). Leproust et al also teach the different densities have the added advantage of reducing disparity in feature areas in different regions of the array (paragraph 0047). Thus, Leprous et al teach the known technique of having different regions have different probe densities.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the probe carrier as taught by

Sheehan et al in view of Ilsley et al so that features within a region have the same probe density and the different regions have different probe densities in accordance with the teachings of Leproust et al to arrive at the instantly claimed probe carrier with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a probe carrier having the added advantage of reducing disparity in feature areas in different regions of the array as explicitly taught by Leproust et al (paragraph 0047). In addition, it would have been obvious to the ordinary artisan that the known technique of having same regions with the same probe density different regions with different probe densities as taught by Leproust et al could have been applied to the probe carrier of Sheehan et al in view of Ilsley et al with predictable results because the known technique of having same regions with the same probe density different regions with different probe densities as taught by Leproust et al predictably results in probe densities for genetic assays.

9. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sheehan et al (Biosensors and Bioelectronics, vol. 18. pages 1455-1459, available online 2 April 2003; as evidenced by the Biosensors and Bioelectronics homepage at sciencedirect.com [retrieved on 2010-02-02]) in view of Ilsley et al (U.S. Patent Application Publication No. US 2004/0081969 A1, published 29 April 2004, filed 29 October 2002) as applied to claim 1 above, and further in view of Ares et al (U.S. Patent Application Publication No. US 2004/0009512 A1, published 15 January 2004, filed 25 April 2003).

Regarding claim 11, the probe carrier of claim 1 is discussed above in Section 7.

Neither Sheehan et al nor Ilsley et al specifically teach the maximum number of spots in the arrays differs 100 to 1000 times.

However, Ares et al teach arrays comprising a plurality of different oligonucleotide spot patterns, wherein each spot pattern is to a different target nucleic acid (paragraph 0072), and that the number of spots of a typical array is about twenty or about twenty thousand (paragraph 0071), which has the added advantage of being useful in high throughput applications (paragraph 0072). Thus, Ares et al teach the known technique of providing spot densities having 1000-fold differences.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the carrier of Sheehan et al in view of Ilsley et al so that range of the number of spots is such that the first area has 20 probes and another area has 20,000 probes as taught by Ares et al to arrive at the instantly claimed carrier with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a carrier having the added advantage of being useful in high throughput applications as explicitly taught by Ares et al (paragraph 0072). In addition, it would have been obvious to the ordinary artisan that the known technique of having spot arrays having ranges of spot numbers of 1000 times difference of Ares et al could have been applied to the carrier of Sheehan et al in view of Ilsley et al with predictable results because the known technique of having spot arrays having ranges of spot numbers of

1000 times difference of Ares et predictably results in a reliable array configuration for detecting target molecules.

Response to Arguments

10. Applicant's arguments with respect to the previous rejections of the claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571)272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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